EXHIBIT F

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/527,844	03/17/2000	Timothy ?. Barberich	4821-334-999	3697

20582 7590 06/18/2003

PENNIE & EDMONDS LLP
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WASHINGTON, DC 20006

EXAMINER	
BAHAR, MOJDEH	

ART UNIT	PAPER NUMBER
1617	19

DATE MAILED: 06/18/2003

AMEND. AFTER FINAL 9·18·03

APPEAL DUE 9·18·03

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/527,844	BARBERICH ET AL.	
	Examiner	Art Unit	
	Mojdeh Bahar	1617	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Applicant's response to the office action of November 5, 2002, and amendment submitted April 4, 2003 is acknowledged.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. abstract (AN 1997: 593623 CAPLUS).

Davis et al. abstract discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al. further discloses that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia, and in reducing anxiety in patients about to undergo dental surgery, see abstract.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. abstract (AN 1997: 593623 CAPLUS) in view of Lowe et al. (USPN 4,831,031), Allen et al. (USPN 5,312,925) and Parkash et al.

Davis et al. abstract discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al. further discloses that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia, and in reducing anxiety in patients about to undergo dental surgery, see abstract.

Davis et al. does not specifically teach metabolites of ziprasidone, amounts (i.e., dosage), routes of administration.

Lowe et al. (USPN 4,831,031) teaches that aryl piperazinyl (C2-C4) alkylene heterocyclic compounds (including ziprasidone) and their pharmaceutically acceptable salts, known neuroleptic agents, can be administered orally, in form of tablets or capsules or parentrally, see col. 3, line 54-col.4 line 33. Lowe et al also teaches that a daily dosage range is from 5 to 500 mg, see in particular col. 4, lines 3-33, see also claims 1-9.

Allen et al. (USPN 5,312,925) specifically teaches the employment of ziprasidone hydrochloride as a neuroleptic agent.

Parkash teaches the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5-HT2 and D2 receptors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders.

One of ordinary skill in the art would have been motivated to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders, because ziprasidone in general and ziprasidone hydrochloride are known neuroleptic agents employed in treating anxiety, depression associated with schizophrenia and situational anxiety (i.e., anxiety prior to dental surgery). Employment of different salts and metabolites of a known active is within the skill of the artisan and therefore obvious.

Response to Arguments

Applicant's arguments filed April 4, 2003 have been fully considered but they are not persuasive. In response to the rejection under 35 USC 102, applicant argues that the instant claims are drawn to a method of employing ziprasidone metabolites and not ziprasidone itself in treating disorders ameliorated by the inhibition of seratonin reuptake and/or dopamine reuptake. As set forth in the previous office action, note that ziprasidone converts to its metabolites *in vivo*. Therefore the administration of ziprasidone results in its conversion to metabolites thereof. Consequently, the administration of ziprasidone necessarily and inherently results in its administration/conversion to ziprasidone metabolites *in vivo*. Therefore each and every element of the claim is indeed met. Applicant then argues that the disclosure of dosage forms in the specification presupposes the existence of a ziprasidone metabolite prior to its administration to a patient. Note that none of the claims rejected under 35 USC 102 recites a dosage form and arguments as to unclaimed limitations are moot. In response to applicant's argument that the

references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inclusion of the metabolites in the dosage forms) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant then argues that there is no motivation to combine the three prior art references used in the obviousness rejection. Applicant argues that none of the three references teaches the employment of ziprasidone metabolites. Note that all references teach the employment of ziprasidone itself and as argued herein above, the employment of the metabolites of ziprasidone would result in the same *in vivo* activity. Therefore following the court's ruling in *Zenith Laboratories Inc. v. Bristol-Myers Squibb Co.*, the Skilled Artisan would know that the compound Ziprasidone is not limited to "its pre-ingested form", 30 USPQ2d 1285, 1289. In the instant case the ziprasidone metabolites are employed to treat disorders ameliorated by the inhibition of seratonin reuptake and/or dopamine reuptake. Ziprasidone itself is known to be useful in treating these diseases via the same mechanisms, therefore it would have been obvious to employ the metabolites in lieu of ziprasidone in treating these same disorders. Applicant further argue and supply the Ereshefsky reference showing that the ziprasidone metabolites are inactive. Note the Parkash et al. reference in the 103 rejection herein above which teaches that ziprasidone sulfone and sulfoxide--though not as active as ziprasidone itself--nevertheless exhibit affinities for 5-HT2 and D2 receptors. Therefore at the very least the particular metabolites taught in Parkash et al. are not inactive.

Applicant then argues against the obviousness rejection, stating that in order for administration of ziprasidone metabolites to result in the same *in vivo* activity as the administration of ziprasidone itself, ziprasidone itself must be inactive. As shown herein above in the Parkash et al. reference, both ziprasidone and its metabolites are known to have affinities for 5-HT2 and D2 receptors, therefore they have the same activity.

Applicant finally argues that Examiner's reliance on Zenith is misplaced. It appears that the applicant argues that the court's reasoning cannot be applicable to the case at bar because Zenith was an infringement case and did not concern anticipation or obviousness. Note that although the case was based on an infringement suit, the court's reasoning is nevertheless applicable to the case at bar since one of the questions before the court was the relation between pre-ingested and ingested form of a drug.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1007. The examiner can normally be reached on (703) 305-1007 from 8:30 a.m. to 6:30 p.m. Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (703) 305-1877. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar
Patent Examiner
June 10, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER 6/14/

Notice of References Cited	Application/Control No. 09/527,844	Applicant(s)/Patent Under Reexamination BARBERICH ET AL.	
	Examiner Mojdeh Bahar	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Parkash et al., Metabolism and Excretion of a New Antipsychotic Drug, ziprasidone, in humans; Drug Metabolism and Disposition vol. 25, no. 7, 1997
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

06/1-/05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: BARBERICH *et al.*

Application No: 09/527,844 Group Art Unit: 1617

Filed: March 17, 2000 Examiner: M. Bahar

For: METHODS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES

Attorney Docket No.: 4821-334-999

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the provisions of 37 C.F.R. §§ 1.191-2, an appeal is taken herein from the final rejection dated June 18, 2003, which rejects claims 1-15 and 50-53 of this application. Appellants submit herewith: (a) an original and two copies of this Appeal Brief; (b) three copies of each Exhibit cited in the Appeal Brief; and (c) a Petition for Extension of Time with provision for the required fee.

I. REAL PARTY IN INTEREST

The real party of interest is the assignee of the above-identified application: Sepracor Inc.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives hereby submit that they are not aware of any appeal or interference which directly affects, will be directly affected by, or will have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 1-15 and 50-53 of this application are under final rejection and are the subject of this appeal. Claims 16-49 were previously canceled without prejudice in response to a Restriction Requirement. Appellants timely filed a "Notice of Appeal from the Primary Examiner to the Board of Patent Appeals and Interferences" on September 30, 2003. The appealed claims are presented in **Exhibit A**, enclosed herewith.

IV. STATUS OF AMENDMENTS

Claims 2 and 6-9 are amended in this paper. The amended claims are fully supported by the specification and claims as filed, and accordingly, no new matter is introduced. A listing of claims, which shows claim amendments made herein and status identifier of each pending claims, is enclosed herewith as **Exhibit A.**

V. SUMMARY OF THE INVENTION

The invention, as recited by the claims on appeal, encompasses a method of treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient which comprises administering to the patient a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate or clathrate thereof. *Id.* at page 5, lines 34-36. Specific disorders that can be treated or prevented using the methods of this invention include neuroleptic disorders, migraines, acute intermittent prophyria, intractable hiccups, Parkinson's disease and epilepsy. *Id.* at page 6, lines 5-10. Specific examples of ziprasidone metabolites are ziprasidone sulfoxide and ziprasidone sulfone. *Id.* at page 6, lines 4-5.

This invention also encompasses a method of treating or prophylaxis of a neuroleptic disorder in a patient which comprises administering to the patient a therapeutically effective amount of either ziprasidone sulfoxide or ziprasidone sulfone, or a pharmaceutically acceptable salt, solvate, hydrate or clathrate thereof. *Id.* at page 6, line 7. Examples of neuroleptic disorders include psychosis, affective disorders, and anxiety. *Id.* at page 6, lines 9-10. Treatment and prophylaxis of various examples of psychosis, affective disorders and anxiety are also claimed. *Id.* at page 6, lines 11-35.

Suitable routes of administration of the compounds of this invention, as well as preferred doses are also encompassed by the claimed invention. *Id.* at page 9, lines 1-13 and lines 33-36.

VI. ISSUES ON APPEAL

A. Rejection of Claims 1-4 and 6-9 Under 35 U.S.C. § 102(b)

One issue presented by this appeal is whether the rejection of Claims 1-4 and 6-9 under 35 U.S.C. § 102(b) over the abstract of Davis is proper, despite the fact that Davis does not disclose, expressly or inherently, all of the limitations recites by the claims on appeal.

B. Rejection of Claims 1-15 and 50-53 Under 35 U.S.C. § 103

A second issue presented by this appeal is whether the rejection of Claims 1-15 and 50-53 under 35 U.S.C. § 103 over Davis, in combination with U.S. Patent No. 4,831,031 to Lowe *et al.* ("Lowe"), U.S. Patent No. 5,312,925 to Allen *et al.* ("Allen") and Prakash *et al.*, *Drug Metabolism and Disposition*, 25(7): 863-872 (1997) ("Prakash"), is proper, despite the fact that none of the references teach or suggest any methods for treating or prophylaxis of a disease or disorder by administering to a patient a ziprasidone metabolite, and other prior art references teach away from the claimed invention.

VII. GROUPING OF CLAIMS

The pending claims do not stand or fall together, but are grouped as follows: claims 1-4 and 6-15; claim 5; claims 50-51; and claims 52-53. Appellants submit that these groups are separately patentable.

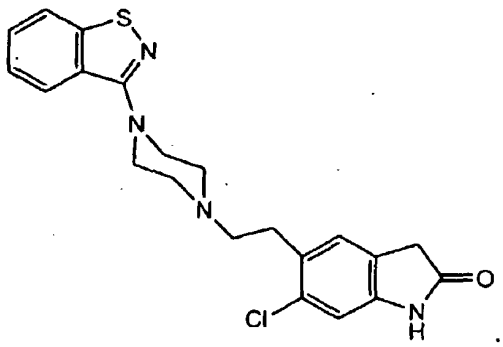
VIII. ARGUMENT

Appellants request that the Board of Patent Appeals and Interferences ("the Board") reverse the Examiner's rejection of the claims on appeal. As discussed below, the Examiner erred in rejecting Claims 1-4 and 6-9 under 35 U.S.C. § 102 over a reference that does not disclose all of their limitations. Furthermore, the Examiner, in rejecting Claims 1-15 and 50-53 under 35 U.S.C. § 103, erred in relying on a combination of references that does not satisfy the legal standards for a *prima facie* case of obviousness. Not only does the combination fail to disclose or suggest all of

the limitations of the claims, one of the references cited by the Examiner, as well as various other prior art references, actually teaches away from the claimed invention.

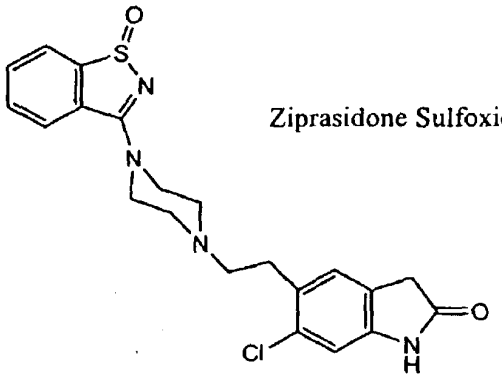
A. Background of the Invention

Ziprasidone hydrochloride is an antipsychotic agent currently commercially available in the United States under the trade name GEODON® (Pfizer Inc.). Ziprasidone is chemically named [5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl-1-yl]ethyl]-6-chlorooxindole]hydrochloride hydrate, and has the following structure:

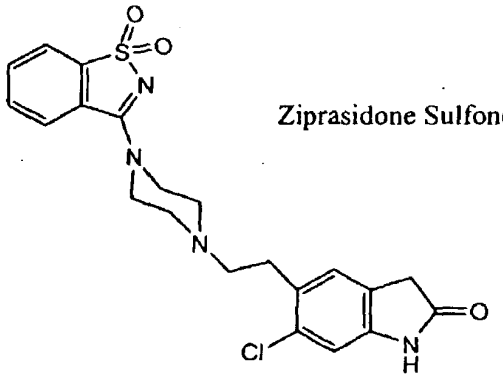


Ziprasidone undergoes complex metabolism, in which at least four major pathways are reportedly involved: 1) N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen; 2) oxidation at sulfur resulting in the formation of sulfoxide or sulfone; 3) reductive cleavage of the benzisothiazole moiety; and 4) hydration of the C=N bond and subsequent sulfur oxidation or N-dearylation of the benzisothiazole moiety. The Specification, page 1, lines 29-34, citing Prakash. At least 12 metabolites have been identified in humans.

Despite the fact that a number of ziprasidone metabolites are known, ziprasidone metabolites in general have been reported to be inactive. *Id.* at page 2, lines 29-31, citing Ereshefsky, *J. Clin. Psychiatry*, 57(suppl.11): 12-25 (1996) ("Ereshefsky"), p. 14. In particular, two metabolites formed by oxidation of the ziprasidone sulfur atom, *i.e.*, ziprasidone sulfoxide and ziprasidone sulfone, were reported to have little contribution to ziprasidone's antipsychotic activity. The structures of these metabolites are shown below:



Ziprasidone Sulfoxide



Ziprasidone Sulfone

While ziprasidone offers a number of benefits, many adverse effects are associated with its administration, including nausea, somnolence, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, male sexual dysfunction and elevated serum liver enzyme levels. *Id.* at page 2, lines 32-36, citing Davis *et al.*, *CNS Drugs*, 8(2): 154-159 (1997) ("Davis").

B. <u>References Relied Upon By the Examiner</u>

The Examiner relies upon Davis in rejecting Claims 1-4 and 6-9 under 35 U.S.C. § 102(b). The Examiner relies upon four references, namely Davis, Lowe, Allen and Prakash, in rejecting the claims under 35 U.S.C. § 103.

Davis, enclosed herewith as **Exhibit B**, reports that ziprasidone has an affinity for 5-HT and D_2 receptors, and can be used to reduce the symptoms of schizophrenia and to reduce anxiety in patients about to undergo dental surgery. Davis, however, does not disclose or suggest ziprasidone metabolites, much less methods of using ziprasidone metabolites *per se* to treat disorders in patients.

Lowe, enclosed herewith as **Exhibit C**, discloses a genus of compounds that encompasses ziprasidone, and their use in the treatment of psychotic

disorders. Lowe, however, does not disclose or suggest ziprasidone metabolites, much less their use.

Allen, enclosed herewith as **Exhibit D**, discloses a monohydrate of ziprasidone hydrochloride and its use as a neuroleptic agent. Allen fails to disclose or suggest ziprasidone metabolites, much less their use in methods of this invention.

Prakash, enclosed herewith as **Exhibit E**, discloses ziprasidone metabolites. However, Prakash actually teaches away from methods of this invention by stating that ziprasidone sulfoxide and ziprasidone sulfone have low affinities for 5-HT_2 and D_2 receptors, and thus are not likely to contribute to ziprasidone's therapeutic activity.

C. The Legal Principles

1. Claim Construction

Claim construction is a question of law within the exclusive province of the court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd.* 116 S.Ct. 1384 (1996). To ascertain the meaning of claims, the court considers the intrinsic evidence: the claims, the specification, and the prosecution history. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman*, 52 F.3d 967. Courts may also consider extrinsic evidence to resolve the scope and meaning of claim terms. *CCS Fitness*, 28 F.3d at 1366.

The words of the claims themselves are the starting point for a claim construction analysis, because the claim language defines the bounds and scope of the protected invention. *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336 (Fed. Cir. 2001); *Johnson Worldwide Assocs. v. Zebco Corp.*, 175 F.3d 985 (Fed. Cir. 1999). "As a general rule, the construing court interprets words in a claim as one of skill in the art at the time of invention would understand them." *Kopykake Enterprises, Inc. v. The Lucks Co.*, 264 F.3d 1377, 1383 (Fed. Cir. 2001) (quoting *Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1555 (Fed. Cir. 1998)); *Rexnord*, 274 F.3d at 1342.

In construing claim language, a court ordinarily "indulge[s] a 'heavy presumption' that a claim term carries its ordinary and customary meaning." *CCS Fitness*, 288 F.3d at 1365 (citing *Johnson Worldwide*, 175 F.3d at 989); *accord, Dow Chem. Co. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1372 (Fed. Cir. 2001) ("As a

starting point, we give claim terms their ordinary and accustomed meaning as understood by one of skill in the art."). In this regard, technical treatises and dictionaries have a special place and can be used to explain the underlying technology and to determine the ordinary meaning of terms in the relevant field. *Id.*; *compare Vitronics Corp.*, 90 F.3d at 1584 n.6 (judges may consult dictionaries and technical treatises at any time "in order to better understand the underlying technology").

Once the court has determined the ordinary art-recognized meaning of a claim term, if such a meaning exists in the art, the next step is to examine the specification to confirm that the patentee has used the term in accordance with its ordinary meaning. *Rexnord*, 274 F.3d at 1342. The same "confirmatory measure" must be performed with the prosecution history. *Id.* at 1343. Thus, "the ordinary meaning of a disputed term, as established by dictionaries or treatises controls 'so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.'" *Kopykake*, 264 F.3d at 1382 (quoting *Vitronics*, 90 F.3d at 1584 n.6).

As recently explained by the Federal Circuit, "claim terms take on their ordinary and accustomed meanings unless the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). Thus, a "claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or the prosecution history." *CCS Fitness*, 288 F.3d at 1366.

2. Anticipation

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 618, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in ... [the] claim." Manual of Patent Examining Procedure ("MPEP") § 2131 (8th Ed., August 2001); and *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). There must be no difference

between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

In the event that a reference does not expressly teach all elements of a claim, anticipation can only be shown by inherency if, and only if, the cited reference makes it clear that the missing descriptive matter is necessarily present in the thing described in the reference. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Company USA Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991)). Inherent anticipation, however, does not require recognition in the prior art. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

Inherency cannot be established by probabilities or possibilities: "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient to support an assertion of inherency." *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)). Therefore, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." MPEP § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in the original).

For example, in cases wherein the parent compound of a metabolite is known in the art, and wherein the metabolite necessarily and inevitably forms from the parent compound under normal conditions, a compound claim directed to the metabolite is anticipated by a prior art reference that discloses the parent compound because "[t]he inherent result of administering [the parent compound] to a patient is the formation of [the metabolite]." *Schering*, 339 F.3d at 1381. However, with proper claiming, patent protection is available for metabolites of known drugs. *Id.* Examples of such proper claiming can include the metabolite in its pure and isolated form, a pharmaceutical composition, or a method of administering the metabolite or the corresponding pharmaceutical composition. *Id.*

3. Obviousness

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir.

1995); *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, the Patent Office must first show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, it must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately found in the prior art, not in an applicant's disclosure. *Deuel*, 51 F.3d at 1558. Third, the Patent Office must show that the prior art teaches or suggests all the claim limitations. MPEP § 2143; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). These criteria must be satisfied with factual and objective evidence found in the prior art: an examiner's conclusory statements cannot form a basis for a *prima facie* case of obviousness. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002).

It is well-established that "a prior art reference must be considered in its entirety, *i.e.*, as a <u>whole</u>, including portions that would lead away from the claimed invention." MPEP § 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (emphasis in the original). Moreover, "in determining whether ... a suggestion can be fairly gleaned form the prior art, the full field of the invention must be considered." *In re Dow Chemical Co.*5 U.S.P.Q.2d at 1531 (Fed. Cir. 1988). One of ordinary skill in the art is charged with the knowledge of all the relevant literature. *Id.* at 1532. Thus, it is improper to view the disclosure of a prior art reference separate from the teachings of others. The determination of obviousness cannot be performed in a vacuum but must be viewed with the understanding of those in the art as a whole. *Cf. Id.* at 1532.

D. <u>Rejection Under 35 U.S.C. § 102(b): The Claims Are Not Anticipated By Davis</u>

The Examiner rejected claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as allegedly anticipated by Davis. The Examiner's rejection is summarized on page 2 of the final Office Action mailed June 18, 2003, enclosed herein as **Exhibit F**, as follows:

> Davis et al. abstract discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al. further discloses that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia, and in

> reducing anxiety in patients about to undergo dental surgery, see abstract.

In response to Appellants' argument that Davis does not teach or disclose the administration of a ziprasidone metabolite to a patient, the Examiner stated:

> [N]ote that ziprasidone converts to its metabolites *in vivo*. Therefore the administration of ziprasidone results in its conversion to metabolites thereof. Consequently, the administration of ziprasidone necessarily and inherently results in its administration/conversion to ziprasidone metabolites *in vivo*. Therefore each and every element of the claim is indeed met.

(Exhibit F, page 4). Appellants disagree with each of the Examiner's contentions for the following reasons.

1. The Examiner's Interpretation of the Term "Administration" is Contrary to its Ordinary Meaning

It is well-established that "claim terms take on their ordinary and accustomed meanings unless the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex* at 299 F.3d 1325. Appellants respectfully submit that the Examiner's interpretation of the term "administration" is flatly contrary to this well settled legal principle.

The pending claims recite methods of treating or prophylaxis of a disorder comprising administering a ziprasidone metabolite to a patient. The claims use the term "administering" in a manner entirely consistent with its conventional meaning, *e.g.*, "to apply as a remedy." The American Heritage College Dictionary, 3rd Ed., page 17 (1997). In other words, a compound that exists outside of the patient is given, or applied to the patient. The Patent Office has long recognized this common meaning. For example, U.S. Patent No. 6,534,507, attached hereto as **Exhibit G**, claims a method for treating psychological disorders by administering a metabolite of the compound gepirone. Numerous other examples exist of issued U.S. patents with claims directed to methods of treating a disorder by administering a metabolite of a known compound.

The Federal Circuit also understands that the term "administration," when used to describe the administration of a metabolite, presumes that the metabolite exists outside of the patient. *See Schering*, 339 F.3d, a copy of which is enclosed herein as **Exhibit H**.

Schering concerned the patentability of claims directed to the compound descarboethoxyloratadine ("DCL") *per se*, a metabolite of the known drug loratadine. (**Exhibit H** at 1375). The record showed that DCL "necessarily and inevitably forms from loratadine under normal conditions." (*Id.* at 1378). Therefore, DCL is "a necessary consequence of administering loratadine to patients." (*Id.*). The court held that a claim directed to the compound DCL itself was anticipated by a prior art patent that disclosed administering loratadine to a patient which results in formation of the compound DCL. However, the court devoted an entire section of its opinion to a discussion of metabolite claims that are patentable:

> [T]his court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs.
>
> * * *
>
> A skilled patent drafter ... might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, ... or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The [prior art] patent would not provide an enabling disclosure to anticipate such claims because, for instance, the [prior art] patent does not disclose isolation of DCL.

(*Id.* at 1381) (emphasis added). In other words, a method of administering a metabolite of a known compound may be patentable even where the metabolite "necessarily and inevitably" forms from the administration of the parent compound.

The term "administration" is used in the specification and claims of this application in a manner entirely consistent with the meaning presumed by the Federal Circuit. Indeed, Appellants never "demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record." *Teleflex* at 299 F.3d 1325. In fact, the term is used in this application in a manner that is completely consistent with its well understood meaning. For example, the specification describes dosage forms

(*e.g.*, tablets and capsules) of ziprasidone metabolites that can be used in methods of the invention. *See, e.g.*, Specification, pages 17-19. There, it is clearly disclosed that a fixed amount of a ziprasidone metabolite is used to prepare the tablets or capsules of the pharmaceutical compositions of this invention. The disclosure of dosage forms presupposes the existence of a ziprasidone metabolite prior to its administration to a patient. Furthermore, the specification discloses the *ex vivo* synthesis and preparation of ziprasidone metabolites at page 8. It is apparent that ziprasidone metabolites, synthesized and prepared using, for example, the methods disclosed in the specification, would exist outside the patient's body.

In sum, the claims pending in this appeal are of the sort expressly permitted by the Federal Circuit. These claims are directed to methods of treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin uptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors comprising the administration of a ziprasidone metabolite. Both the Federal Circuit and Patent Office have recognized that claims such as these claims do not encompass the administration of the parent drug.

The Examiner alleged that Appellants' reliance on *Schering* is misplaced because while *Schering* "explains that a metabolite in its isolated and/or pure form is not anticipated by the drug itself, ... no pure or isolated metabolite of ziprasidone is claimed herein." Advisory Action of September 12, 2003, enclosed herein as **Exhibit I**, page 2. However, the *Schering* court expressly stated that the "administration" of a metabolite of a known drug can be patentable. (**Exhibit H** at 1381). Clearly, the *Schering* court recognized, like those of ordinary skill in the art and other Patent Office examiners, that the "administration" of a metabolite can be patentable precisely because the term presumes existence of the metabolite outside of the patient's body.

In view of well understood meaning of "administration," none of Claims 1-4 and 6-9 are anticipated by Davis. This is because Davis does not disclose the existence of ziprasidone metabolites, much less their existence outside the human body or their administration to a patient. Therefore, Davis does not anticipate any of the claims on appeal. Appellants respectfully submit that the Examiner's rejection of Claims 1-4 and 6-9 under 35 U.S.C. § 102(b) cannot be maintained, and thus respectfully request the Board to reverse the rejection.

2. The Examiner's Interpretation of the Term "Administration" is Contrary to Unambiguous Statements Made by Appellants During Prosecution

As discussed above, the rejection of the claims under 35 U.S.C. § 102 is improper in view of the Examiner's unfounded assertion that the term "administration" encompasses *in vivo* conversion. This assertion is based on an understanding of the meaning of "administration" that is contrary to its ordinary meaning. However, even assuming, for the sake of argument, that the Examiner's understanding of the term is consistent with its ordinary meaning, it is legally improper for the Examiner to maintain the rejection in view of statements made by Appellants during the prosecution of this application.

It is well settled that a patentee can act as his or her own lexicographer and accord a term a meaning different from its conventional one: a "claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or the prosecution history." *CCS Fitness*, 288 F.3d at 1366 (emphasis added). Appellants clearly indicated that the term "administration" or "administering," as used in the claims, means giving to a patient a compound as it exists outside of the body. (*See, e.g.*, The Response of April 4, 2003, enclosed herein as **Exhibit J**, page 3). Therefore, even if Appellants' use of the term "administration" differs from the conventional meaning of the term, the Examiner has no legal basis upon which to reject the pending claims. *Cf. CCS Fitness*, 288 F.3d at 1366. For this additional reason, Appellants respectfully request the Board to reverse the Examiner's rejection of Claims 1-4 and 6-9 under 35 U.S.C. § 102(b).

E. Rejection Under 35 U.S.C. § 103: The Claims Are Not Obvious

The Examiner first rejected claims 1-15 and 50-53 under 35 U.S.C. § 103 as allegedly obvious over Davis in view of Lowe and Allen. The Examiner's rejection is summarized below:

> Davis et al. abstract discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al. further discloses that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia, and in reducing anxiety in patients about to undergo dental surgery, see abstract.

> Davis et al. does not specifically teach metabolites of ziprasidone, amounts (i.e., dosage), routes of administration.
> Lowe ... teaches that aryl piperazinyl (C2-C4) alkylene heterocyclic compounds (including ziprasidone) and their pharmaceutically acceptable salts, known neuroleptic agents, can be administered orally, in form of tablets or capsules or parenterally... Lowe et al also teaches that a daily dosage range is from 5 to 500 mg ... Allen ... specifically teaches the employment of ziprasidone hydrochloride as a neuroleptic agent.
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to ziprasidone or any of its known salts *or metabolites* in a method of treating neuroleptic disorders.

(Office Action of November 5, 2002, enclosed herein as **Exhibit K**, page 3) (emphases added).

Subsequently, in response to Appellants' argument that ziprasidone metabolites were describe by the prior art as inactive, the Examiner alleged that Prakash "teaches the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5-HT2 and D2 receptors." (**Exhibit F**, page 3). According to the Examiner, because Prakash teaches that ziprasidone sulfone and sulfoxide, "though not as active as ziprasidone itself," nevertheless exhibit affinities for 5-HT_2 and D_2 receptors, "at the very least the particular metabolites taught in Prakash et al. are not inactive." (*Id.* at page 5). Based on this, the Examiner contended that "both ziprasidone and its metabolites are known to have affinities for 5-HT2 and D2 receptors, therefore they have the same activity." (*Id.* at page 6) (emphasis added).

The Examiner first relied on an incorrect interpretation of *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 30 U.S.P.Q.2d 1285 (Fed. Cir. 1994). In particular, the Examiner contended that *Zenith* evidences that "the Skilled Artisan would know that the compound Ziprasidone is not limited to 'its pre-ingested form'." (*Id.* at page 5). Even after Appellants pointed out that *Zenith* concerned infringement, not patentability, the Examiner alleged that "the court's reasoning is nevertheless applicable to the case at bar since one of the questions before the court was the relation between pre-ingested and ingested form of a drug." (*Id.* at page 6).

Appellants disagree with each of the Examiner's contentions for the following reasons. Furthermore, while all of the following arguments are applicable to all groups of pending claims, it is believed that claim 5 is separately patentable

from claim 1 (and dependent claims 2-4 and 6-15) because it recites the use of specific metabolites ziprasidone sulfoxide and ziprasidone sulfone, which are not recited by claim 1. As discussed in Section VIII.E.2, below, Prakash specifically teaches away from the use of ziprasidone sulfoxide and ziprasidone sulfone. Therefore, Appellants submit that claim 5, which recites the use of these specific ziprasidone metabolites, is separately patentable.

It is further believed that claims 50-51 and 52-53, which recite the treatment or prophylaxis of a neuroleptic disorder using ziprasidone sulfoxide and ziprasidone sulfone, respectively, are separately patentable from claims 1 and 5 because those limitations are not recited by claim 1 or 5. Prakash specifically teaches away from the use of ziprasidone sulfoxide and ziprasidone sulfone. In addition, none of the references cited by the Examiner disclose the use of these metabolites for the treatment or prophylaxis of a neuroleptic disorder as recited by claims 50-51 and 52-53. For this reason, Appellants submit that claims 50-51 and 52-53 are separately patentable.

1. The Cited References Do Not Teach or Suggest the Claimed Invention

As the Examiner recognized, the primary reference Davis "does not specifically teach the metabolites of ziprasidone." (**Exhibit K**, page 3). Despite this fact, the Examiner rejected the pending claims based on a combination of Davis, Lowe and Allen. None of these references, however, teach or suggest ziprasidone metabolites.

Relying on Lowe and Allen's disclosure of neuroleptic activity of ziprasidone salts, the Examiner contended that it would have been obvious to employ ziprasidone or any of its known salts or metabolites in treating neuroleptic disorders. (*Id.*). A salt form of a compound, however, is completely different from a metabolite of the compound.[1] Therefore, the rejection, insofar as it is based on the Examiner's

[1] Whereas it is well known that a salt form of a compound often has the same pharmacological activity of the compound itself, a metabolite of that compound, which usually involves substantial chemical modification (*e.g.*, deletion, addition or replacement of covalently attached chemical groups) does not necessarily have pharmacological properties identical to the parent compound. *See, e.g.*, Hawley's Condensed Chemical Dictionary, 13th Ed., (John Wiley & Sons, New York, NY, 1997), p.p. 717 and 981. Thus, a blanket assertion that use of a salt or a metabolite of ziprasidone would have been obvious, merely because a ziprasidone salt was known to be active, is entirely devoid of scientific and factual support.

unsupported, factually incorrect and conclusory statement, cannot be maintained. *See In re Sang-Su Lee*, 277 F.3d at 1343-4.

Prakash does not cure the deficiency. Prakash is an evaluation of pharmacokinetics of ziprasidone in four human patients, focusing on determining the metabolic pathways of ziprasidone and its metabolites and pharmacokinetic parameters thereto (**Exhibit E**, page 863). Prakash does not evaluate the pharmacological effects of any ziprasidone metabolite, or even comment on such for ten of twelve metabolites identified. Only in the abstract does Prakash comment on the pharmacology of the sulfoxide and sulfone metabolites, due to their unusual metabolic pathway and presence in human serum. Specifically, Prakash discloses that "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone," and goes on to state that these metabolites are "thus unlikely to contribute to [ziprasidone's] antipsychotic effects." (*Id.* at page 863, Abstract col.2, lines 10-11) (emphases added). Therefore, when considered in its entirety, Prakash does not teach anything about the pharmacology of most ziprasidone metabolites, but does teach that the sulfoxide and sulfone ziprasidone metabolites are not effective antipsychotic agents. *See W.L. Gore & Associates*, 721 F.2d at 1548.

In light of the fact that Davis, Lowe and Allen do not even disclose or suggest ziprasidone metabolites, and that Prakash teaches that ziprasidone metabolites, in particular ziprasidone sulfoxide and ziprasidone sulfone, are ineffective antipsychotic agents, it is evident that the combination of these four references does not teach or suggest the claimed invention. Thus, Appellants respectfully request the Board to reverse the Examiner's rejection of the claims under 35 U.S.C. § 103.

2. Prakash, As Well As Other Prior Art References, Teaches Those Skilled in the Art Away from the Claimed Invention

In response to Appellants' argument that none of the Davis, Lowe and Allen teach or suggest ziprasidone metabolites, the Examiner relied on a single sentence taken from Prakash: "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone." (**Exhibit E**, page 863, Abstract col. 2, lines 10-12). Interpreting this sentence to mean that ziprasidone sulfone and sulfoxide do have affinities for 5-HT_2 and D_2 receptors, the

Examiner contended that it would have been obvious to employ ziprasidone metabolites in a method of treating neuroleptic disorders. (**Exhibit F**, pages 3-4).

Further, the Examiner's reliance on a single sentence, taken without consideration of the reference as a whole, is improper. *See W.L. Gore & Associates*, 721 F.2d at 1548. This is readily apparent when one looks beyond the single sentence relied upon by the Examiner, and sees that Prakash teaches that ziprasidone's antipsychotic effects are not due to the sulfoxide and sulfone metabolites ("the affinities of [the metabolites] for 5-HT2 and D2 receptors are low ... and are thus unlikely to contribute to [ziprasidone's] antipsychotic effects."). (**Exhibit E**, page 863, Abstract col. 2, lines 10-12). Prakash's conclusion is consistent with the disclosure of Ereshefsky, as well as Physician's Desk Reference, 56th Ed., page 2688 (2002) ("PDR"), copies of which are enclosed herewith as **Exhibits L** and **M**, respectively. Both references teach that the activity of ziprasidone is due to ziprasidone itself, not its metabolites.

To put it in a different way, even assuming that one of ordinary skill in the art could conclude from Prakash that ziprasidone sulfone and sulfoxide have an affinity for 5-HT_2 and D_2 receptors as the Examiner contends, such a conclusion cannot form a basis in rejecting claims as allegedly obvious. MPEP § 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) ("a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." (emphasis in original)). This is because the question is not whether these metabolites were known to demonstrate some *in vitro* activity, but whether those of ordinary skill in the art, reading Prakash, would have been motivated to use these metabolites to treat a neuroleptic disorder. By expressly stating that ziprasidone sulfoxide and ziprasidone sulfone do not contribute to the antipsychotic effect of ziprasidone, Prakash itself, as well as Ereshefsky and PDR, clearly evidence that they would not have been.

3. The Examiner's Assertions are Scientifically and Factually Unsupported

In the Office Action of November 5, 2002, the Examiner, in response to Appellants' argument that none of Davis, Lowe and Allen teach the use of ziprasidone metabolites, alleged that because all of the references teach the

employment of ziprasidone itself and ziprasidone converts *in vivo* to the metabolites, "the employment of the metabolites of ziprasidone would result in the same *in vivo* activity." (**Exhibit K**, page 4) (emphasis added). In response to this unfounded assertion, Appellants pointed out that in order for the administration of a ziprasidone metabolite to result in the same *in vivo* activity as the administration of ziprasidone itself, either ziprasidone must be entirely converted to an active metabolite or ziprasidone itself must be inactive. Neither is actually the case. (**Exhibit J**, page 5).

The Examiner, apparently misunderstanding Appellants' argument, responded that "[a]s shown ... in the Prakash et al. reference, both ziprasidone and its metabolites are known to have affinities for 5-HT2 and D2 receptors, therefore they have the same activity." (**Exhibit F**, page 6). Thus, the Examiner seems to believe that because ziprasidone and its metabolites have affinities for the same type of receptors, they exhibit the same *in vivo* pharmaceutical effect. This is not correct and is contrary to well-established principles of pharmacology.

The only way by which the administration of ziprasidone could result in the same *in vivo* activity as the administration of a ziprasidone metabolite would be if ziprasidone itself were inactive, since, as with any drugs, the effect of ziprasidone administration is due to all pharmaceutically active compounds that result from its administration. It is clear, however, that ziprasidone is pharmaceutically active. Indeed, Prakash, Ereshefsky and PDR report that the antipsychotic effect obtained from the administration of ziprasidone is primarily due to the activity of ziprasidone itself. Therefore, it is evident that the administration of ziprasidone cannot result in the same *in vivo* activity as the administration of a ziprasidone metabolite.

In sum, Appellants submit that the pharmacokinetics and pharmacologies of ziprasidone and its metabolites are sufficiently different as evidenced, for example, by the degree of affinities for 5-HT_2 and D_2 receptors, which is disclosed in Prakash itself. Therefore, the Examiner's blanket assertion that the administration of a ziprasidone metabolite would result in the same *in vivo* activity as the administration of ziprasidone is without any factual or scientific basis. Thus, the rejection of the claims under 35 U.S.C. § 103 should be reversed and withdrawn. *See In re Sang-Su Lee*, 277 F.3d at 1343-4.

4. **The Examiner's Reliance on *Zenith* is Misplaced**

To support the proposition that the cited references Davis, Lowe and Allen disclose the use of ziprasidone metabolites, the Examiner alleged that these references teach the employment of ziprasidone itself and "the employment of ziprasidone metabolites would result in the same *in vivo* activity." (**Exhibit F**, page 5). In doing so, the Examiner relied on *Zenith*. In particular, the Examiner alleged that *Zenith* evidences that "the Skilled Artisan would know that the compound Ziprasidone is not limited to its 'pre-ingested form'." (*Id.*).

Appellants pointed out that *Zenith* is not applicable in this case because: 1) *Zenith* provides no evidence of what was known prior to this invention about the biological activity of ziprasidone or its metabolites; and 2) *Zenith* concerned whether the *in vivo* conversion of cefadroxil DC into cefadroxil monohydrate would constitute an infringement of a patent, not whether the claims of the patent were anticipated or obvious. (**Exhibit J**, page 5). In response, the Examiner alleged that although *Zenith* was "based on an infringement suit, the court's reasoning is nevertheless applicable to the case at bar since one of the questions before the court was the relation between pre-ingested and ingested form of a drug." *See Schering* (**Exhibit F**, page 6). This allegation is simply incorrect.

Contrary to the Examiner's allegation, *Zenith* addressed the relationship between pre-ingested and ingested form of cefadroxil only in the context of patent infringement, *i.e.*, whether the *in vivo* formation of cefadroxil monohydrate would infringe a claim directed to that hydrate. The case did not concern the patentability of a hydrate, much less a metabolite. Indeed, the *Zenith* court expressly stated that "[t]he question before us is *not one of validity*: whether the claim would be patentable over the prior art ... The question here is one of infringement." *Zenith*, 30 U.S.P.Q.2d at 1289 (emphasis added). Moreover, since *Zenith*, the Federal Circuit has made it clear that the prior art disclosure of a compound does not preclude the patentability of claims directed to the administration of its metabolites. (**Exhibit H** at 1381).

In sum, the Examiner's rejection of the claims under 35 U.S.C. § 103 should be withdrawn for factual and legal reasons.

CONCLUSION

Claims 1-4 and 6-9 are not anticipated by Davis, which does not disclose the metabolites of ziprasidone, much less methods of using ziprasidone metabolites. The Examiner's interpretation of the term "administration," which would encompass *in vivo* formation of a compound resulting from the administration of the parent compound, is entirely contrary to the term's well-accepted meaning and the way the term is used in the specification. Moreover, even assuming, *arguendo*, that the Examiner's interpretation of the term is consistent with its well-accepted meaning, Appellants have made it abundantly clear during the prosecution of this application that the term "administration" does not encompass the *in vivo* conversion of ziprasidone. *See CCS Fitness*, 288 F.3d at 1366.

Claims 1-4 and 6-15 are not obvious over the combination of Davis, Lowe, Allen and Prakash. Davis, Lowe and Allen do not disclose or suggest the administration of ziprasidone metabolites, and Prakash actually teaches away from the administration or use of ziprasidone metabolites. The Examiner's rejection of the claims is based on assertions that are factually and scientifically unfounded, as well as a misplaced reliance on *Zenith*.

Claims 5, 50-51 and 52-53 are not obvious over the combination of Davis, Lowe, Allen and Prakash for substantially the same reasons. Claim 5 is further nonobvious because Prakash specifically teaches away from the use of ziprasidone sulfoxide and ziprasidone sulfone.

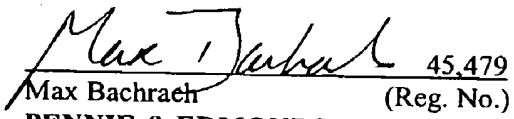
Claims 50-51 are further nonobvious because Prakash specifically teaches away from the use of ziprasidone sulfoxide, and none of the references cited by the Examiner disclose the use of ziprasidone sulfoxide for the treatment or prophylaxis of a neuroleptic disorder.

Claims 52-53 are further nonobvious because Prakash specifically teaches away from the use of ziprasidone sulfone, and none of the references cited by the Examiner disclose the use of ziprasidone sulfone for the treatment or prophylaxis of a neuroleptic disorder.

Thus, it is respectfully submitted that the final rejections of claims 1-15 and 50-53 under 35 U.S.C. §§ 102 and 103 are in error and warrant reversal by the Board.

Respectfully Submitted,

Date: December 30, 2003



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